

Investigator Initiated Study
Clinical Study Report
**Anti-Androgen Treatment for COVID-19 (GT0918 –
Proxalutimide)**

Protocol:	KP-DRUG-SARS-001
Status:	Approved
Approval date:	15 September 2020
Prepared by:	John McCoy, PhD
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NCT number:	04446429
GCP compliance:	This study was conducted in compliance with Good Clinical Practice, including the archival of essential documents.
Co-Principal Investigators	Flavio Cadegiani, MD, Andy Goren, MD, Carlos Wambier, MD
Date study initiated:	15 September 2020 (first informed consent signed)
Date study completed	24 December 2020 (clinical data cut-off)
Report date:	January 19, 2021

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SYNOPSIS

Sponsor Name:

Investigator initiated study

Investigational Drug Name:

Proxalutamide (GT0918)

Study Title:

Anti-Androgen Treatment for COVID-19

Regulatory Oversight:

Brazilian National Ethics Committee (Approval number 4.173.074; CAAE 34110420.2.0000.0008; Comitê de Ética em Pesquisa (CEP) of the Comitê Nacional de Ética em Pesquisa (CONEP) of the Ministry of Health (MS)) (CEP/CONEP/MS). Clinicaltrials.gov NCT04446429

Investigators:

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2. Andy Goren, MD: Applied Biology, Inc.
3. Carlos Wambier, MD: Brown University, RI, USA

Study Centers:

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Site 002
Exame Imagem e laboratorio
Sgas 915, Lote 69/70, Lojas 157/158, 157 - Asa Sul
Brasília - Df, 70200-610

Study Period:

September 15, 2020 December 24, 2020

Objectives:

The primary objective of this study is to demonstrate superiority of proxalutamide versus standard of care in preventing hospitalization of males diagnosed with COVID-19 in an outpatient setting.

Methodology:

Prospective, interventional, placebo controlled, double-blinded, randomized parallel assignment study

Number of Patients:

The number of subjects required to power the study was estimated to be 127 subjects in each arm (254 subjects total). 262 subjects were randomized into the study and 262 subjects complete the study.

Diagnosis and Inclusion Criteria:**Inclusion Criteria:**

- Male
- Age ≥ 18 years old
- Positive SARS-CoV-2 rtPCR test in the past 7 days
- Not hospitalized for acute respiratory symptoms
- Patients with adequate bone marrow, liver and renal function,
- Serum creatinine $\leq 1.5 \times \text{ULN}$ or creatinine clearance ≥ 60 mL/min (calculated using Cockcroft-Gault formula)
- Coagulation: INR $\leq 1.5 \times \text{ULN}$, and APTT $\leq 1.5 \times \text{ULN}$
- Written informed consent obtained prior to any screening procedures

Exclusion Criteria:

- Subject enrolled in a study to investigate a COVID-19 drug
- Subject taking an anti-androgen of any type including: androgen deprivation therapy, 5-alpha reductase inhibitors, etc...
- Patients who are allergic to the investigational product or similar drugs (or any excipients);
- Subjects who have malignant tumors in the past 5 years, with the exception of completely resected basal cell and squamous cell skin cancer and completely resected carcinoma in situ of any type;
- Subjects with known serious cardiovascular diseases, congenital long QT syndrome, torsade de pointes, myocardial infarction in the past 6 months, or arterial thrombosis, or unstable angina pectoris, or congestive heart failure

which is classified as New York Heart Association (NYHA) class 3 or higher, or left ventricular ejection fraction (LVEF) < 50%, QTcF > 450 ms

- Subjects with uncontrolled medical conditions that could compromise participation in the study (e.g. uncontrolled hypertension, hypothyroidism, diabetes mellitus)
- Patients who have taken part in an experimental drug study within 4 weeks of initiating this study treatment
- Known diagnosis of human immunodeficiency virus (HIV), hepatitis C, active hepatitis B, treponema pallidum (testing is not mandatory)
- Not willing or unable to provide informed consent

Duration of treatment: 30 days

Reference therapy, dose and mode of administration:

Standard of care (treatment was optional as per local health care recommendations)

- Azithromycin 500mg q.d 5 days
- Nitazoxanide 500mg b.i.d 6 days
- Dipyrrone 1g t.i.d (if needed)
- Paracetamol 750mg t.i.d. (if needed)
- Ondansetron 8mg t.i.d (if needed)
- Dexamethasone 6mg q.d. (if needed)

Criteria for evaluation:

Primary Endpoint: COVID-19 hospitalization [Time Frame: 30 days]; Percentage of subjects hospitalized due to COVID-19

Safety: Treatment emergent adverse events

Statistical methods:

The statistical method employed to analyze the data will be the Chi-squared test for independent proportions.

Notes:

1. The method employed is the "N-1" Chi-squared test as recommended by Campbell (2007) and Richardson (2011).
2. The confidence interval is calculated according to the recommended method given by Altman et al. (2000).

References:

1. Altman DG, Machin D, Bryant TN, Gardner MJ (Eds) (2000) Statistics with confidence, 2nd ed. BMJ Books. (p. 49)
2. Campbell I (2007) Chi-squared and Fisher-Irwin tests of two-by-two tables with small sample recommendations. Statistics in Medicine 26:3661-3675.
3. Richardson JTE (2011) The analysis of 2 x 2 contingency tables - Yet again. Statistics in Medicine 30:890.

Summary - Conclusions:

Efficacy Results

Proxalutamide was evaluated as a treatment for non-hospitalized COVID-19 subjects. As of the date of this report, 128 subjects in the control group and 134 subjects in the proxalutamide group completed the study. The statistical evaluation was conducted on a 2x2 contingency table. The combined analysis of the raw data for all sites is presented in Table 1.

H0: the proportion of subjects hospitalized due to COVID-19 in the proxalutamide arm is equal to the proportion of subjects hospitalized due to COVID-19 in control arm

HA: the proportion of subjects hospitalized due to COVID-19 in the proxalutamide arm is less than the proportion of subjects hospitalized due to COVID-19 in the control arm

Mathematically written as:

H0: $p_1 - p_2 = 0$

HA: $p_1 - p_2 < 0$

The results indicate the following:

Combined sites 001-002 (all subjects): a Chi-square test was performed to determine whether the treatment (proxalutamide, placebo) was associated with hospitalization rates in COVID-19 patients. The proportion of COVID-19 patients hospitalized was significantly different between the proxalutamide and control arms; $\chi^2(1) = 42.051$, $p < .0001$. The difference in proportions was 27.30% with a 95%CI: [19.79%, 35.59%]; thus, the null hypothesis is rejected.

	Placebo	Proxalutamide
Not Hospitalized	93	134
Hospitalized	35	0
Total	128	134

Table 1. Clinical outcomes of COVID-19 male patients treated with proxalutimide compared to placebo.

Safety Results:

No proxalutamide related serious adverse events were observed during the study. Gastrointestinal treatment emergent adverse events were more frequent among the proxalutamide arm compared to the placebo arm. Two patient have died in the placebo arm.

Conclusion:

Treatment of COVID-19 patients with proxalutamide was significantly ($p < 0.0001$) associated with reduced rate of hospitalization.

Limitations:

Due to the fact that this is an outpatient study, compliance of patients to medications is a limitation; however, even if subjects have not completed the dosing schedule or returned to study site, hospitalization data is accurate. This is due to the fact that in Brazil hospitalization of COVID-19 patients participating in clinical studies is reported by the national health care system. In addition, the standard of care was not applied consistently between sites and Principal Investigators. No other limitations have been identified as of the date of Dec 24, 2020.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADT	Androgen deprivation therapy
AE	Adverse event
AGA	Androgenetic alopecia
ALT	Alanine aminotransferase
AR	Androgen receptor
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate aminotransferase
AUC _{ss}	Area under the concentration x time curve at steady state
BICR	Blinded independent central review
BSA	Body surface area
CFR	Code of Federal Regulations
C _{0h,ss}	Pre-dose concentration at steady state
CHMP	Committee for Medicinal Products for Human Use
C _{maxss}	Maximum concentration at steady state
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
EMA	European Medicines Agency
FDA	Food and Drug Administration of the United States
FDHT	Fluor α dihydrotestosterone
GCP	Good clinical practice
GnRH	Gonadotropin-releasing hormone
Hb	hemoglobin
HR	Hazard ratio
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
ITT	Intent-to-treat population
IV	intravenous

MedDRA	Medical Dictionary for Regulatory Activities
MRU	Medical resource utilization
pK	pharmacokinetics
PRO	Patient-reported outcomes
PSA	Prostate-specific antigen
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
US	United States of America
WBC	White blood cell

ETHICS

Independent Ethics Committee/Institutional Review Board

The study protocol and amendments were reviewed by an Independent Ethics Committee or Institutional Review Board depending on the country's regulations.

Ethical Conduct of the Study

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Known instances of nonconformance were documented and are not considered to have had an impact on the overall conclusions of this study.

Subject Information and Consent

Subjects or their legally acceptable representatives provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment. Known instances of nonconformance were documented and are not considered to have impacted the overall conclusions of this study.

Personal data from subjects enrolled in this study were limited to those data necessary to investigate the efficacy, safety, quality, and utility of the investigational study agent(s) used in this study, and were collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Additional information on the ethical conduct of this study is contained in the Ethical Aspects section of the protocol.

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Co-Principal Investigators	Flavio Cadegiani, MD Andy Goren, MD Carlos Wambier, MD
Project Scientist(s)	John McCoy, PhD*
Clinical Laboratories	DASA Laboratorios da America Brasilia, Brazil
Data and Study Monitoring	Andrija Stanimirovic, MD, PhD Maja Kovacevic, MD

Note:

* Author of this report

1. INTRODUCTION

Early in the COVID-19 pandemic, reports from Wuhan, China demonstrated that the infectivity and severity of the disease disproportionately affects men. Of patients sampled in the early stages of the outbreak 42% were female versus 58% male.¹ Now that the disease has progressed to the majority of countries across the globe, the trend has been demonstrated many times over; men are more likely to be infected, more likely to have severe disease, and have a greater case fatality rate compared to women.² Lifestyle differences and gender-biased comorbidities, e.g., incidence of smoking and hypertension, have been suggested as contributing to this gender discrepancy,² however, definitive proof of these associations is lacking. Alternatively, it has been suggested that the male bias in COVID-19 disease severity may be linked to androgens.^{3,4}

SARS-CoV-2 entry into type II pneumocytes is dependent on modification of a viral spike protein by the transmembrane protease, serine 2 (TMPRSS2) expressed on the surface of human cells.⁵ The only known promoter of the TMPRSS2 gene in humans is an androgen response element located in the 5' promoter region.⁶ It would follow that reducing the expression of TMPRSS2 by blocking the androgen receptor would decrease SARS-CoV-2 entry into human cells. In several observation studies, the androgen-mediated phenotype of androgenetic alopecia (AGA) has been linked to COVID-19 disease severity.^{3,4} In a cohort of 122 men hospitalized with COVID-19, 79% were diagnosed with AGA compared to the expected prevalence of 31-53% in aged matched controls of similar ethnicity.³ Additionally, it has been demonstrated that COVID-19 disease severity was directly correlated with AGA progression; men with higher Hamilton-Norwood stages were more likely to experience severe disease and death.⁷

Further evidence connecting COVID-19 to androgens has been reported in prostate cancer patients undergoing androgen deprivation therapy (ADT). Montopoli et al. studied a large population of COVID-19 patients in northern Italy, observing that COVID-19 infection rates were lower in prostate cancer patients receiving ADT compared to prostate cancer patients not receiving ADT (OR 4.05; 95% CI 1.55-10.59).⁸ Other groups have suggested that polycystic ovary syndrome may also indicated increase risk of severe COVID-19 disease in women,⁹ and a recent study supported this hypothesis.¹⁰ Finally, it has been suggested that variations in the androgen receptor gene may contribute to the racial variations in case fatality rates observed in the United States.¹¹ Taken together, there is growing body of evidence to support that SARS-CoV-2 infectivity is mediated by the androgen receptor and will likely respond to drugs that reduce androgen receptor function.

5-alpha-reductase inhibitors (5ARis) are commonly prescribed for androgenetic alopecia and benign prostatic hyperplasia; they block the conversion of testosterone to the more potent androgen, dihydrotestosterone (DHT).¹² In two retrospective cohort studies 5-alpha-reductase inhibitors (5ARi) have been shown to provide

protection for men with COVID-19.¹³ In a study of 77 men hospitalized with COVID-19 it was found that among men taking 5ARis, 8% were admitted to the ICU compared to 58% of men not taking 5ARis ($P = 0.0015$). In the cohort, 5ARis were associated with reduced risk for ICU admissions RR 0.14 (95% CI: 0.02–0.94).¹³ Similarly, it was demonstrated that the frequency of COVID-19 symptoms was drastically reduced for men using 5ARis in an outpatient setting. A statistically significant ($p < 0.05$) reduction in the frequency of 20 of the 29 clinical symptoms was observed in AGA men using 5ARis compared to AGA men not using 5ARis. For example, 38% and 2% of men presented with low-grade fever, 60% and 6% with dry cough, and 88% and 15% reported anosmia in the non-5ARi and 5ARi groups, respectively.¹⁴

In the studies referenced above the 5ARi used was dutasteride. Dutasteride is only indicated for men and has a warning prohibiting its use in women. Proxalutamide (GT0918) is a novel second generation androgen receptor antagonist that has several distinct advantages as a therapy for SARS-CoV-2. Proxalutamide demonstrates a dual mechanism of action. It is highly effective antagonist of AR as well as exhibiting pharmacological effects of inducing the down-regulation of AR expression. This second mechanism is not present in similar drug of this class, for example, bicalutamide or enzalutamide. Because of the dual mechanism of action, it is expected to be a more effective and less toxic second-generation anti-androgen drug therapy. Clinical evidence has demonstrated that proxalutamide lowers AR expression and activity. Additionally, it has been reported that proxalutamide lowers the expression of ACE2. Both would be beneficial for preventing SARS-CoV-2 entry into lung cells. Finally, the sponsor has studied proxalutamide safety in both men and women, making it an ideal candidate for a broadly applied therapeutic for SARS-CoV-2 infection and COVID-19 disease.

2. OBJECTIVES

The primary purpose of this study is to evaluate the efficacy of proxalutamide as a treatment for COVID-19 male outpatients.

2.1. Primary Objective

To demonstrate the superiority of proxalutamide over placebo in reducing the rate of COVID-19 hospitalizations within 30 days after initiation of treatment.

2.2. Secondary Objectives

To demonstrate the superiority over placebo in the COVID-19 Ordinal Outcomes Scale on 15 and 30 days after treatment. The COVID-19 Ordinal Scale defined as:

8. Death;
7. Hospitalized, on invasive mechanical ventilation or ECMO;
6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;

5. Hospitalized, requiring supplemental oxygen;
4. Hospitalized, not requiring supplemental oxygen- requiring ongoing medical care (COVID-19 related or otherwise);
3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
2. Not hospitalized, limitation on activities;
1. Not hospitalized, no limitations on activities

3. METHODS

3.1. Overview of Study Design

3.1.1. Overall Design

This was a randomized, double-blind, placebo-controlled study of proxalutamide compared with placebo in subjects with laboratory confirmed primary SARS-CoV-2 infection. The planned total sample size was approximately 254 subjects randomized in a 1:1 ratio (127 subjects in the proxalutamide arm and 127 subjects in the placebo arm).

The study consisted of a screening phase of up to 2 days before randomization to establish eligibility, a double-blind treatment phase (15-day treatment cycles; continuous dosing), and a long-term follow-up (30 days). Proxalutamide or matched placebo along with standard of care was to be administered orally on a continuous daily dosing schedule at a starting dose of 200 mg per day. The dosage was selected based on preclinical projections of Phase 2 study (Appendix 2). The optimal biological dose was combined with safety and the pK/pharmacodynamic profiles observed during the Phase 1.

Subjects were treated as outpatients and followed per the normal hospital and clinic protocols for COVID-19 patients. In the event of worsening symptoms patients returned to the hospital and were re-evaluated by the PI. If warranted, patients were admitted to the hospital. Subjects who discontinued treatment for any reason were entered in to the long-term follow-up phase of the study. A flow chart describing patients in the study is provided in Fig. 1.

Safety assessment was based on reported adverse events, clinical laboratory tests, vital sign measurements and physical examinations.

An Independent Data Monitoring Committee (IDMC) consisting of independent experts in the fields of biostatistics and viral diseases, evaluated unblinded safety and efficacy data from the study at prespecified intervals as described in the protocol.

The efficacy and safety results of the study are located in the main text of this report. Additional detailed summary tables are included in the Attachments section located at the end of the main text.

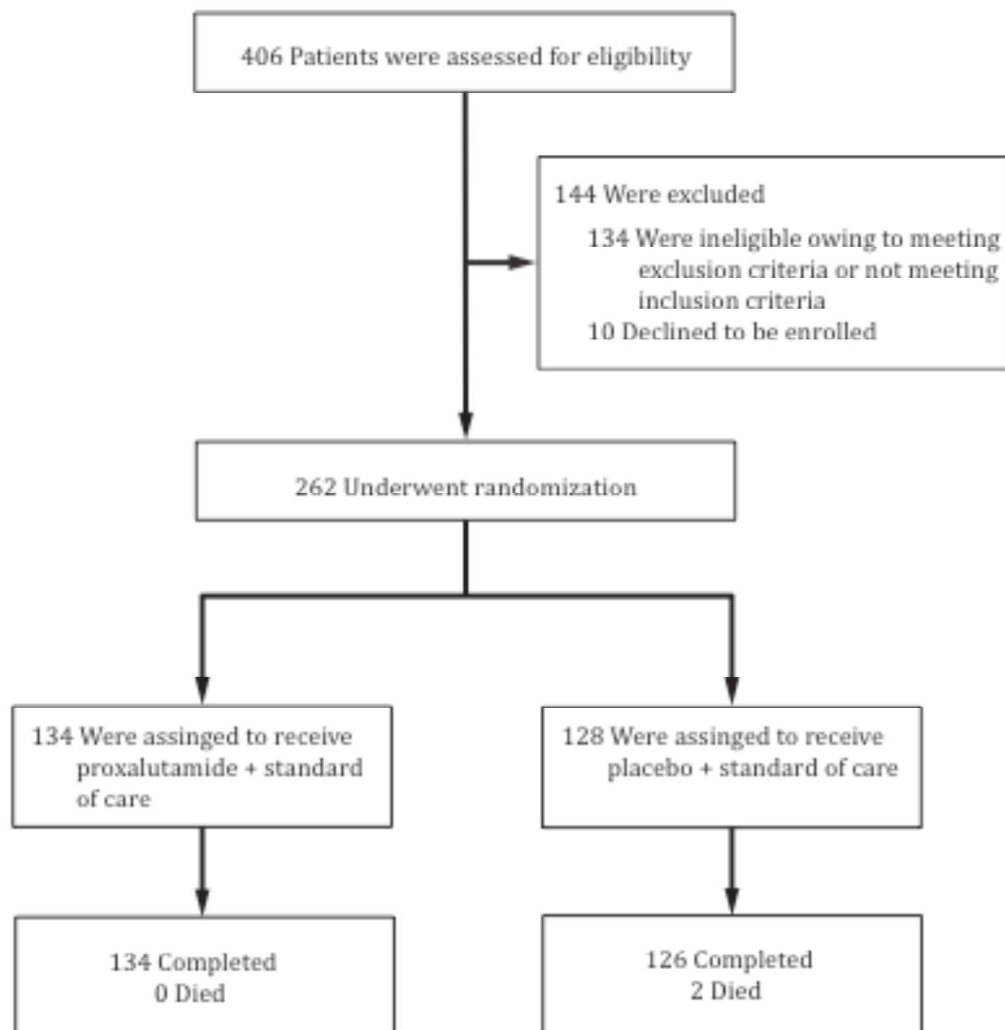


Figure 1. Flow of patients in the study.

3.1.2. Changes in Conduct

There were three amendments to the protocol. Changes are summarized in Table 1.

Amendment 001	Removal of dutasteride arm	December 1, 2020
Amendment 002	Substitution of ivermectin with nitazoxanide	September 10, 2020
Amendment 003	Change the age for inclusion	September 10, 2020

Table 1. Amendments to the protocol

3.2. Study Population

3.2.1. Overview

The study population was composed of males 18 years or older that were non-hospitalized SARS-CoV-2 confirmed subjects presenting to an outpatient hospital and/or clinic participating in the local health care electronic record exchange (SUS).

3.2.2. Inclusion Criteria

Subjects enrolled in this study were required to meet the following key acceptance criteria:

- Male age ≥ 18 years old
- Laboratory confirmed positive SARS-CoV-2 rtPCR test within 7 days prior to randomization
- Clinical status on the COVID-19 Ordinal Scale (defined in Section 5.1) of 1 or 2
- Coagulation: INR $\leq 1.5 \times \text{ULN}$, and APTT $\leq 1.5 \times \text{ULN}$
- Subject (or legally authorized representative) gives written informed consent prior to any study screening procedures
- Subject (or legally authorized representative) agree that subject will not participate in another COVID-19 trial while participating in this study

3.2.3. Exclusion Criteria

Subjects were not to be enrolled into the study if it was determined upon pre-study examination that they met the following key criteria:

- Subject enrolled in a study to investigate a treatment for COVID-19
- Subject taking an anti-androgen of any type including: androgen deprivation therapy, 5-alpha reductase inhibitors, etc...
- Patients who are allergic to the investigational product or similar drugs (or any excipients);

- Subjects who have malignant tumors in the past 5 years, with the exception of completed resected basal cell and squamous cell skin cancer and completely resected carcinoma in situ of any type
- Subjects with known serious cardiovascular diseases, congenital long QT syndrome, torsade de pointes, myocardial infarction in the past 6 months, or arterial thrombosis, or unstable angina pectoris, or congestive heart failure which is classified as New York Heart Association (NYHA) class 3 or higher, or left ventricular ejection fraction (LVEF) < 50%, QTcF > 450 ms
- Subjects with uncontrolled medical conditions that could compromise participation in the study (e.g. uncontrolled hypertension, hypothyroidism, diabetes mellitus)
- Known diagnosis of human immunodeficiency virus (HIV), hepatitis C, active hepatitis B, treponema pallidum (testing is not mandatory)
- Alanine Transaminase (ALT) or Aspartate Transaminase (AST) > 5 times the upper limit of normal.
- Estimated glomerular filtration rate (eGFR) < 30 ml/min
- Severe kidney disease requiring dialysis
- Subject unlikely to return for day 15 site visit for reasons other than remission
- Subject (or legally authorized representative) not willing or unable to provide informed consent

3.3. Removal of Subjects from Therapy or Assessment

Subject participation could be discontinued before completing the study for any of the following reasons:

- The principal investigator or the site monitor believes a subject is at risk of injury
- An adverse event related to the study treatment

3.4. Study Agents Information

- Proxalutamide and the matching placebo were provided [REDACTED]
- Azithromycin, Nitazoxanide, Dipyrone, Paracetamol, Ondansetron, Dexamethasone were provided by EMS Industria Farmaceutica. Sao Paulo, Brazil

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

3.4.2. Issues Identified for the Investigational Product During the Study

There were no issues identified during the course of the study.

3.5. Randomization and Blinding

Eligible patients were be randomized into the proxalutamide or placebo arm during the enrollment phase. Each subject was assigned a subject study number. The first subject was assigned the number 001 and each subject thereafter will be assigned a consecutive number i.e., 002, 003, etc. The randomization plan was based on a 1:1 ratio for each arm. Since the study was double-blinded, the following randomization schedule was used but the identification of the arm assignment was only known by the study monitor:

- Subjects 001-020 will be assigned to Arm 1
- Subjects 021-040 will be assigned to Arm 2
- Subjects 041-060 will be assigned to Arm 1
- Subjects 061-080 will be assigned to Arm 2
- Subjects 081-100 will be assigned to Arm 1
- Subjects 101-120 will be assigned to Arm 2
- etc.....

Unblinding of treatment assignment during the study for safety reasons occurred for 5 subjects; however, the PI at the site was not unblinded only the site monitor.

3 subjects received equal dosages of arm A and arm B but were not included in the analysis.

3.6. Dosage and Administration

Subjects were to start administration of study drug after randomization.

Proxalutamide 200 mg (2 x 100 mg tablets) or matching placebo orally once daily with or without food. Standard of care was offered to all subjects. Standard of care (treated as per local health care recommendations)

- Azithromycin 500mg q.d 5 days
- Nitazoxanide 500mg b.i.d 6 days
- Dipyrone 1g t.i.d (if needed)
- Paracetamol 750mg t.i.d. (if needed)
- Ondansetron 8mg t.i.d
- Dexamethasone 6mg q.d. (if needed)

3.6.1. Dose Modifications

Subjects that have experienced complete remission were permitted to stop treatment prior to 14 days.

3 subjects received equal dosages of arm A and arm B but were not included in the analysis.

3.7. Treatment Compliance

Treatment compliance was monitored by phone on day 1, 2, 3 and 5, 7 and 14. An accurate and current accounting of the dispensing of the study drug for each subject was maintained on an ongoing basis by the Investigator or his/her designated personnel. The number of study drug tablets dispensed to the subject was recorded on the Investigational Product Accountability Log. Compliance as to taking the treatment with or without food was not monitored.

3.8. Prior and Concomitant Therapy

Every medication or treatment taken by the subject during the study and the reason for administration was recorded on the CRF.

3.8.1. Prohibited Therapies

Medications known to antagonize the androgen receptor or decrease androgen receptor function were prohibited in the study (per the exclusion criteria) included herbal (eg, saw palmetto) and non-herbal products. Use of 5- α reductase inhibitors, estrogens and any other anti-cancer therapy was not allowed during study (per the exclusion criteria).

3.8.2. Restricted Therapies

Proxalutamide showed no significant inhibition on CYP1A2 and CYP2E1, weak inhibition on CYP2D6, CYP2C9, CYP2C19 and CYP3A (midazolam), but obvious inhibition on CYP3A4 (testosterone). Potential inducer on CYP3A4 at a concentration of 10 μ M. No inductive effects on CYP1A2 and CYP2B6 were observed in the level of enzymatic activity. Co-administration of strong/moderate CYP3A4 inducer, strong/moderate CYP3A4 inhibitor, sensitive CYP3A4/ CYP2D6 substrates and narrow therapeutic index with proxalutamide were restricted.

3.9. Study Evaluations

3.9.1. Time and Events Schedule

The investigator will assesses each subject and record the efficacy parameters at baseline, days 15 and 30 following enrollment (+/-3 days).

3.9.2. Efficacy Evaluations

The following efficacy parameters were assessed and recorded in the CRF:

I. COVID-19 Hospitalization: COVID-19 hospitalization [Time Frame: 30 days]
Percentage of subjects hospitalized due to COVID-19

II. COVID-19 Ordinal Outcome Scale: COVID-19 Ordinal Outcomes Scale on Day 15, 30 [Time Frame: assessed on study day 15, 30]

We will determine the COVID Ordinal Scale for all patients on study day 15, 30

COVID Ordinal Scale defined as:

8. Death;
7. Hospitalized, on invasive mechanical ventilation or ECMO;
6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
5. Hospitalized, requiring supplemental oxygen;
4. Hospitalized, not requiring supplemental oxygen- requiring ongoing medical care (COVID-19 related or otherwise);
3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
2. Not hospitalized, limitation on activities;
1. Not hospitalized, no limitations on activities

3.9.3. Efficacy Criteria

All efficacy criteria are gathered during routine clinical exam and recorded in CRF. Hospitalization for subjects that discontinued early was monitored till day 30 from initiation of treatment using the Brazilian national health care surveillance system. The system monitors all hospitalizations for COVID-19 clinical trial participants.

[REDACTED]

[REDACTED]

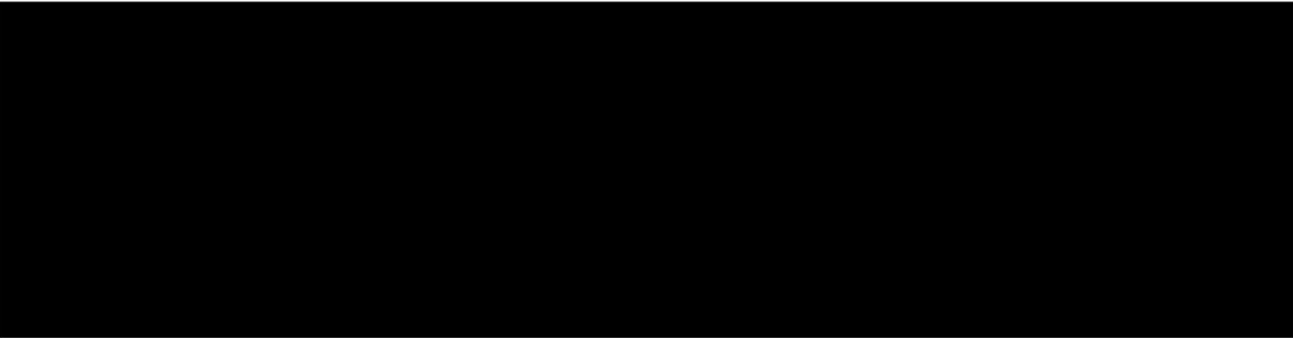
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[REDACTED]

[REDACTED]



3.9.5. Safety Evaluations

Safety was evaluated based on the following variables:

- TEAEs graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03
- Clinical laboratory tests (hematology, serum chemistry, lipid panel, TSH)
- Vital sign measurements
- Physical examinations
- Medical history
- Concomitant medications and procedures

The timing of all safety procedures is described in the Time and Events Schedule located in the study protocol (Appendix 1).

3.9.5.1. Adverse Events

Adverse event definitions, attributions, and severity criteria are listed in the protocol (Appendix 1). All adverse events were to be described and recorded in the appropriate CRF including date of onset, seriousness, severity, outcome and action taken, and relationship to study treatment as assessed by the investigator. Serious or unexpected adverse events were to be reported as specified in the protocol.

3.9.5.3. Clinical Laboratory Tests

Safety evaluation in this study included the following clinical laboratory tests:

- Hematology: hemoglobin (Hb), red blood cell (RBC) count, white blood cell (WBC) count, platelets, WBC differential count (absolute values for neutrophils, lymphocytes, monocytes, eosinophils, basophils);
- Chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Note: if > 1.5 x ULN, include analysis of direct and indirect bilirubin), blood urea nitrogen (BUN) or urea, calcium, creatinine, magnesium, potassium, sodium, glucose, lactate, C-Reactive Protein (CRP) and erythrocyte sedimentation rate (ESR);
- Hormones: Total testosterone, Sex Hormone Binding Globulin (SHBG), dihydrotestosterone (DHT), estradiol
- SARS-CoV-2 rtPCR Ct and qualitative result

Samples for these clinical laboratory tests were obtained at the times indicated in the in the protocol (Appendix 1). All clinical laboratory tests were analyzed by a central laboratory.

For unexplained or unexpected clinically significant laboratory test values, the test(s) were to be repeated as soon as possible and followed up until the results had returned to the normal range or until an adequate explanation for the abnormality was found.

3.9.5.3. Other Safety Observations

At screening, a complete physical examination, including, SARS-CoV-2 rtPCR test was to be performed. Baseline characteristics, comorbidities, test results, and medications used were recorded. For each subject, the age, frequency and duration of medication used and the following pre-existing conditions were recorded: type 2 diabetes, hypertension, obesity (BMI) and chronic obstructive pulmonary disease (COPD). During subsequent visits, either a full or abbreviated physical exam was performed. New abnormal physical exam findings were to be documented.

3.10. Data Quality Assurance

The investigators and hospital/clinic were to permit trial-related monitoring, audits, IRB/IEC(s) review and regulatory inspection(s) by providing direct access to source data/documentation. Every effort was to be made to keep staff assignments consistent throughout the entire study. The PI who assessed the subject at baseline was to follow the subject throughout the completion of the study. The study was to be conducted and that data generated, documented (recorded), and reported was in compliance with the study protocol (Appendix 1), with GCP, and any other applicable regulatory requirements. The study monitor was to audit the study procedures and CRFs throughout the study.

3.11. Statistical Methods

The primary objective of the study was to evaluate the efficacy of proxalutimide compared to placebo in non-hospitalized COVID-19 male patients. The primary end point was the rate of hospitalization (COVID-19 Ordinal Outcomes Scale >3, Appendix 1) by day 30.

General Principles:

- Double-blinded, placebo controlled randomized interventional study with a two-sided type I error rate of 0.05.
- Continuous variables will be expressed as median (interquartile range [IQR]) and categorical variables will be expressed as a number
- 95% confidence intervals will be calculated for the primary outcome
- Group comparisons will be analyzed by χ^2 test

- The placebo arm will be used as a reference group when calculating treatment effects
- Statistical analyses will be conducted using XLSTAT version 2020.5.1 (Addinsoft, Inc.)

3.11.1. Analysis Populations

- The primary analysis will be based on the intent-to-treat (ITT) population. The data from all subjects enrolled in the study will be analyzed.
- The safety analysis will be based on a modified intent-to-treat (MITT) population i.e., subjects who received at least one dosage of the interventional treatment.
- Subgroup analysis based on: age stratification

3.11.2. Sample Size Determination

Assumptions:

- Riccardo et al (2020)¹⁵ reported that in Italy the hospitalization rate was as high as 20% among adults above the age of 65 tested positive for SARS-CoV-2. Further, Montopoli et al (2020)¹⁶ reported that males represent 60% of hospitalized patients; therefore, we can estimate that the rate of hospitalization of males over the age of 65% tested positive for SARS-CoV-2 is approximately 30%.
- To estimate the efficacy of Proxalutamide as a treatment for COVID-19, we use the results reported by Montopoli et al (2020)¹⁶. According to Montopoli et al: "Comparing the total number of SARS-CoV-2 positive cases, patients with prostate cancer receiving ADT had a significantly lower risk of SARS-CoV-2 infections compared to patients who did not receive ADT (OR 4.05; 95% CI 1.55-10.59). Applying the 20% hospitalization rate, we derive a probability of treatment efficacy of 50%

$$p_{treatment} = \frac{OR \times p_{control}}{1 + OR \times p_{control} - p_{control}} :$$

- The study has two arms with randomization at 1:1 ratio
- 80% power to detect the difference in proportions using a two-tailed test with a type I error rate of 5%
- 5% of the subjects will not complete the study (at least 1 dosage)

Sample Size Estimate:

Based on the assumptions above, we calculated¹⁷ that at a minimum we would need to recruit 254 subjects i.e., 127 subjects in each arm

3.11.3. Planned Analyses

A single final analysis was planned for the primary endpoint and secondary endpoints after 254 subjects had completed treatment. Interim efficacy and safety data was performed upon recruitment of at least 50% of the subjects as per the study protocol (Appendix 1).

3.11.3.1. Efficacy

Efficacy analyses were performed for the ITT population, using the randomization stratification factors as documented in the study protocol (Appendix 1).

3.11.3.1.1. Primary Endpoint

The primary endpoint was percentage of subjects hospitalized due to COVID-19 over the time frame of 30 days post randomization.

The χ^2 test for independent proportions was used to perform the analysis of the primary end point. The null and alternative hypothesis are given below:

H0: the proportion of subjects hospitalized due to COVID-19 in the proxalutamide arm is equal to the proportion of subjects hospitalized due to COVID-19 in control arm

HA: the proportion of subjects hospitalized due to COVID-19 in the proxalutamide arm is less than the proportion of subjects hospitalized due to COVID-19 in the control arm

Mathematically written as:

H0: $p_1 - p_2 = 0$

HA: $p_1 - p_2 < 0$

3.11.3.1.2. Secondary Endpoints

As a secondary measure the change from baseline in the COVID Ordinal Scale for all patients was determined on study day 15 and study day 30.

The COVID Ordinal Scale is defined as:

- 8. Death;
- 7. Hospitalized, on invasive mechanical ventilation or ECMO;
- 6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
- 5. Hospitalized, requiring supplemental oxygen;
- 4. Hospitalized, not requiring supplemental oxygen- requiring ongoing medical care (COVID-19 related or otherwise);
- 3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
- 2. Not hospitalized, limitation on activities;

- 1. Not hospitalized, no limitations on activities

3.11.3.1.3. Other Endpoints

No other endpoint were reported in the study

3.11.3.2. Safety

3.11.3.2.1. Adverse Events

The definitions and standard for reporting adverse events are described in the study protocol (Appendix 1). Treatment emergent adverse events (TEAEs), vital sign measurements, and deaths reported during the study were to be summarized using the safety population.

There were no serious adverse events (drug related) during the course of the study.

3.11.3.2.2. Laboratory Abnormalities

Only data collected by the laboratory used for the clinical study were to be summarized. Normal ranges were used to identify values considered as abnormal laboratory results

3.11.3.3. Medical Resource Utilization

Data for medical resource utilization for hospitalized clinical study participants was received from the Regional Hospital Asa Norte Brasilia, Brazil

3.11.4. Changes in Planned Analyses

There were no changes in the planned analysis

4. SUBJECT AND TREATMENT INFORMATION

All subjects in this study, regardless of treatment arm, received concurrent standard of care treatment for COVID-19 prescribed by the Principal Investigator. Subjects who received proxalutamide plus standard of care referred to in results sections text as the "proxalutamide arm" and in tables as "Proxalutamide." Subjects who received placebo plus standard of care are referred to in results section text as the "placebo arm" and in tables as "Placebo." The standard of care treatment were drugs recommended by the local health care authorities in Brazil. The Principal Investigator offered the following drugs to subjects as standard-of-care therapy: Azithromycin 500mg per day for 5 days combined with Nitazoxanide 500mg every 12 hours for 5 days, pro re nata (PRN) medications: antipyretic agents: dipyrone and acetaminophen, antiemetic agent: ondansetron if needed and dexamethasone if needed. Compliance to standard-of-care therapy was not evaluated.

4.1. Subject Disposition and Study Completion/Withdrawal Information

All subjects randomized to either the placebo or treatment arms completed the study. The term completed as used herein refers to the hospitalization status at day

30. Two subjects died during the course of the study but were included in the data set analyzed.

4.2. Demographic and Baseline Characteristics

Four hundred six (406) subjects signed the informed consent and were screened; 262 subjects were randomized (Figure 1). Of the 144 patients who were ineligible, 134 did not qualify based on the study inclusion/exclusion criteria, 10 subjects declined to participate. Demographic characteristics (Table 3) were well balanced between the two arms. The median age of subjects was 44.5 years. It is important to note that since the study was conducted in Brazil, the population is ethnically diverse and the majority of subjects did not identify themselves as Caucasian, black or Asians.

4.3. Prior and Coexisting Medical Conditions

Among the patients randomized to the study, coexisting medical conditions were documented. Variables most likely to affect COVID-19 disease outcomes are reported below for the placebo and treatment arms (Table 3), including hypertension, dyslipidemia, diabetes, pre-diabetes, obesity, asthma, myocardial infarction and COPD.

Characteristic	All (N=262)	Proxalutamide (N=134)	Placebo (N=128)
Age — yr	44.5 ± 7.7	44.2 ± 14.0	45.0 ± 10.8
No. of coexisting conditions — no. /total no. (%)			
None	158/262 (60)	74/134 (53)	84/128 (66)
One	49/262 (19)	29/134 (22)	20/128 (16)
Two or more	55/262 (21)	31/134 (23)	24/128 (19)
Coexisting conditions — no./total no. (%)			
Type 2 diabetes	21/262 (8)	11/134 (8)	10/128 (8)
Hypertension	55/262 (21)	33/134 (25)	22/128 (20)
COPD	1/262 (0)	1/134 (1)	0/128 (0)
Obesity	43/262 (16)	22/134 (16)	21/128 (16)

Table 3. Baseline characteristics of the two study groups.

4.4. Protocol Deviations

No protocol deviations have been made.

4.5. Treatment Compliance

All of the subjects randomized to the study completed the trial i.e., hospitalization status was obtained through day 30. All subjects randomized to receive the active

Proxalutamide had taken at least 3 dosages (as confirmed by follow-up at the site or by phone). Compliance with standard of care was not monitored during the study i.e., Azithromycin and Nitazoxanide combination, Dipyrone, Paracetamol, Ondansetron and Dexamethasone. It is likely that not all subjects have complied with these treatments.

5. EFFICACY RESULTS

5.1. Data Sets Analyzed

Efficacy analyses were performed using the ITT population, which included 262 randomized subjects (134 subjects in the proxalutamide arm and 128 subjects in the placebo arm). Analyses were performed for rate of hospitalization for the treatment group versus the placebo group. Secondary analysis was conducted comparing the percentage of subjects in each category of the COVID-19 Ordinal Outcomes Scale 15 and 30 days after treatment.

5.2. Primary Efficacy Analysis: Percentage of subjects hospitalized due to COVID-19 after 30 days

A statistically significant reduction in the percentage of subjects hospitalized due to COVID-19 was observed in men taking proxalutamide (0%) compared to the placebo (standard of care) (27%), ($p < 0.001$). Thirty five subjects were hospitalized in the control group compared to zero in the proxalutamide group (Table 4). The proportion of COVID-19 patients hospitalized was significantly different between the proxalutamide and control arms; $\chi^2(1) = 42.051$, $p < .0001$. The difference in proportions was 27.30% with a 95%CI: [19.79%, 35.59%]. No patient receiving proxalutamide died compared to 2 (1.56%) in the control group.

	Placebo	Proxalutamide
Not Hospitalized	93	134
Hospitalized	35	0
Total	128	134

Table 4. Clinical outcomes of COVID-19 men treated with Proxalutimide compared to standard of care.

5.3. Secondary Endpoint Analyses: COVID-19 Ordinal Outcome Scale

COVID-19 disease progression was tracked over 30 days using the COVID-19 Ordinal Outcomes Scale for patients in the proxalutamide and placebo arms. Data at day 15 and 30 were recoded for each subject. The COVID Ordinal Scale defined as:

- 8. Death;
- 7. Hospitalized, on invasive mechanical ventilation or ECMO;

6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
5. Hospitalized, requiring supplemental oxygen;
4. Hospitalized, not requiring supplemental oxygen- requiring ongoing medical care (COVID-19 related or otherwise);
3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
2. Not hospitalized, limitation on activities;
1. Not hospitalized, no limitations on activities

Score on ordinal scale — no. (%)	Baseline			Day 15			Day 30		
	All	Proxalutamide	Placebo	All	Proxalutamide	Placebo	All	Proxalutamide	Placebo
1. Not Hospitalized, no limitation on activities	160/262 (61)	63/134 (47)	97/128 (76)	212/262 (81)	134/134 (100)	78/128 (61)	234/262 (89)	134/134 (100)	100/128 (78)
2. Not Hospitalized, limitations on activities**	102/262 (39)	71/134 (53)	31/128 (24)	26/262 (10)	0/134 (0)	26/128 (20)	14/262 (5)	0/134 (0)	14/128 (11)
3. Hospitalized, not requiring supplemental oxygen, no longer requires ongoing medical care (Covid-19-related or otherwise)	0/262 (0)	0/134 (0)	0/128 (0)	0/262 (0)	0/134 (0)	0/128 (0)	1/262 (0)	0/134 (0)	1/128 (1)
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19-related or otherwise)	0/262 (0)	0/134 (0)	0/128 (0)	3/262 (1)	0/134 (0)	3/128 (2)	8/262 (3)	0/134 (0)	8/128 (6)
5. Hospitalized, requiring supplemental oxygen	0/262 (0)	0/134 (0)	0/128 (0)	12/262 (5)	0/134 (0)	12/128 (9)	1/262 (0)	0/134 (0)	1/128 (1)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	0/262 (0)	0/134 (0)	0/128 (0)	4/262 (2)	0/134 (0)	4/128 (3)	0/262 (0)	0/134 (0)	0/128 (0)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	0/262 (0)	0/134 (0)	0/128 (0)	5/262 (2)	0/134 (0)	5/128 (4)	2/262 (1)	0/134 (0)	2/128 (2)
8. Death	0/262 (0)	0/134 (0)	0/128 (0)	0/262 (0)	0/134 (0)	0/128 (0)	2/262 (1)	0/134 (0)	2/128 (2)

Table 4. COVID-19 Ordinal Scale at Baseline, 15 and 30 Days after treatment

Table 5 describes the tabulation of all subjects at baseline, day 15 and day 30.

5.4. Efficacy Summary

In COVID-19 male outpatients (COVID-19 8-point ordinal scale <3), the proxalutamide (GT0918) demonstrated a significant reduction in the rate of hospitalization.

6. SAFETY RESULTS

6.1. Data Sets Analyzed

Summaries of adverse events and other safety data are based on the safety population that comprises the 262 subjects who received at least 1 dose of either proxalutamide or placebo (134 subjects in the proxalutamide arm and 128 subjects in the placebo arm).

6.2. Adverse Events

All TEAEs whether serious or non-serious, were reported from the time informed consent was obtained until 30 days after the last dose of study treatment (unless subjects died or had complete remission and did not respond to follow-up).

6.2.1. Summary of All Adverse Events

Treatment-emergent adverse events were reported for 34% of subjects in the proxalutamide arm and for 61% of subjects in the placebo arm. SAEs were only reported in the placebo arm.

	Placebo	Proxalutamide
Safety population	128	134
Number of subjects with TEAE	78	45
Number of subjects with SAEs	35	0
Number of subjects with TEAE leading to discontinuation	0	0
Number of subjects with TEAE leading to death	2	0

Table 6. Summary of all adverse events

6.2.2. Most Frequently Reported Adverse Events

The most frequently reported TEAEs (i.e., occurring in $\geq 10\%$ of subjects in either arm) were Dehydration (15% proxalutamide versus 14% placebo), back pain (10% proxalutamide versus 12% placebo). Gastrointestinal TEAE were more frequent in the proxalutamide arm: Diarrhea (21% proxalutamide versus 9% placebo), Nausea (14%

proxalutamide versus 6% placebo), Abdominal pain (12% proxalutamide versus 5% placebo)

	Placebo	Proxalutamide
Safety population	128	134
Number of subjects with 1 or more TEAE		
System organ class		
Gastrointestinal		
Diarrhea	11	28
Nausea	8	19
Abdominal pain	7	16
Vomiting	1	4
Abdominal discomfort	8	12
Dyspepsia	3	15
Heartburn	2	8
General		
Fatigue	57	3
Fever	26	5
Disease progression	69	7
Cardiac		
Tachycardia	11	4
Nervous system		
Headache	12	3
Ageusia	15	5
Anosmia	17	6
Metabolism and nutrition		
Dehydration	18	20
Ear and labyrinth		
Ear pain	13	8

Musculoskeletal and cognitive tissue		
Arthralgia	7	2
Back pain	15	13
Scrotal pain	3	1
Pain in extremity	4	6
Respiratory, thoracic and mediastinal		
Shortness of breath	46	6
Skin and subcutaneous tissue		
Lesions	6	3

Table 7. Summary of most frequently reported adverse events

6.2.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

6.2.3.1. Deaths

Deaths within 30 days of enrollment in the study was reported for 2 subjects (1.6%) in the placebo arm. No deaths were reported in the proxalutamide arm. In the placebo arm, the primary cause of death was reported as progressive COVID-19 disease.

6.2.3.2. Serious Adverse Events

The percentage of subjects reported to have SAEs was 0% (0/134) in Proxalutamide arm and 27% (35/128) in the placebo arm.

6.3. Clinical Laboratory Evaluation

Not available as of the date of this report.

6.4. Safety Summary

No SAEs were reported during the course of the study in the proxalutamide arm. Gastrointestinal TEAE more common in the proxalutamide arm compared to the placebo arm. This could be due to a possible interaction between proxalutamide and nitazoxanide.

7. DISCUSSION

Men infected with SARS-CoV-2 have an increased risk of severe COVID-19 disease compared to women.² A multitude of factors may contribute to the gender

disparity,² however, evidence^{3,4,7,8} to support that androgens may be involved in the regulation of COVID-19 disease severity. Concurrently, the mechanism of action is likely androgen receptor regulation of the expression of the TMPRSS2 enzyme, one of the enzymes utilized by SARS-CoV-2 to enter type II pneumocytes in human lungs.⁵

Here we demonstrate in a randomized, double-blinded, placebo controlled, interventional study that men in outpatient setting treated with proxalutamide, a novel second generation androgen receptor antagonist experience a significantly lower rate of hospitalization ($p < 0.001$) compared to the standard of care.

It is of importance to note that the compliance with the standard of care was not monitored or applied consistently between sites and Principal Investigators; however, in clinical trials none of the treatments offered as standard of care have shown to be effective as a treatment for COVID-19. In particular, in a randomized controlled study by Rocco et al (2020) concluded that: "In patients with mild Covid-19, symptom resolution did not differ between nitazoxanide and placebo groups after 5 days of therapy"¹⁸.

8. CONCLUSIONS

In COVID-19 male outpatients (NIAID COVID-19 8-point ordinal scale < 3), proxalutamide (GT0918) demonstrated a significant reduction in the rate of hospitalization. No SAEs were reported during the course of the study in the proxalutamide arm. Gastrointestinal TEAE more common in the proxalutamide arm compared to the placebo arm.

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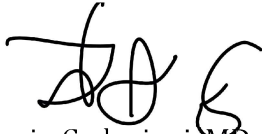
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SIGNATURE OF RESPONSIBLE MEDICAL PERSONNEL



Flavio Cadegiani, MD

19 Jan 2021

Date



Andy Goren, MD

19 Jan 2021

Date



Carlos Wambier, MD

19 Jan 2021

Date

APPENDIX 1 – Study Protocol

CLINICAL STUDY PROTOCOL

Anti-Androgen Treatment for COVID-19 (Proxalutamide - GT0918)

Proprietary and Confidential

The information contained in this document is confidential and proprietary to the principal investigators. It is offered with the express agreement that you will not disclose this document to any other person(s), or discuss the information contained herein or make reproduction by any means electronic or mechanical, or use it for any purpose other than the evaluation of the proposed clinical study for approval by an Institutional Review Board.

PROTOCOL NAME:

Clinical Study: Anti-Androgen Treatment for COVID-19

PROTOCOL IDENTIFYING NUMBER:

KP-DRUG-SARS-001

PROTOCOL VERSION NUMBER:

1.30

PROTOCOL VERSION DATE:

December 1, 2020

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GENERAL INFORMATION

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TBD

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**Protocol signature page
Investigator's Agreement**

Clinical Study: Anti-Androgen Treatment for COVID-19

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Name	Signature	Date
Flavio A. Cadegiani, MD, MSc, PhD		
Andy Goren, MD		

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List of Abbreviations

CFR	Code of Federal Regulations
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IRB	Institutional Review Board
EC	Ethics Committee
HCP	Healthcare Professional
CDC	US Center for Disease Control
SAE	Serious Adverse Event
AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
UP	Unanticipated Problem

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1. Background

1. Overview

During the continuing SARS-CoV-2 (COVID-19) pandemic, several studies have reported a significant difference in the rate of severe cases between adult females and adult males (42% vs 58%).¹ Among children under the age of 14, the rate of severe cases was reported to be extremely low.¹ To explain this difference, several theories have been proposed including cigarette smoking and lifestyle habits. However, no theory fits both the gender difference in severe cases as well as reduced risk in pre-pubescent children. Our past research on male androgenetic alopecia (AGA) has led us to investigate an association between androgens and COVID-19 pathogenesis.² In normal subjects, androgen expression demonstrates significant variation between men and women as well as between adults and pre-pubescent children.

SARS-CoV-2 primarily infects type II pneumocytes in the human lung. SARS-CoV-2 enters pneumocytes, by anchoring to the ACE2 cell surface receptor. Prior to receptor binding, viral spike proteins undergo proteolytic priming by the transmembrane protease, serine 2 (TMPRSS2).³⁻⁵ TMPRSS2 inhibition or knock down reduces ability of SARS-CoV-1 (a related virus to SARS-CoV-2) to infect cells in vitro.⁶ Additionally, TMPRSS2 also facilitates entry of influenza A and influenza B into primary human airway cells and type II pneumocytes.⁷

The human TMPRSS2 gene has a 15 bp androgen response element and in humans, androgens are the only known transcription promoters for the TMPRSS2 gene.⁸⁻¹⁰ In a study of androgen-stimulated prostate cancer cells (LNCaP), TMPRSS2 mRNA expression increase was mediated by the androgen receptor.¹⁰ Further, the ACE2 receptor, also critical for SARS-CoV-2 viral infectivity, is affected by male sex hormones with higher activity found in males.¹¹

Previously, we have reported the results from two retrospective cohort analysis demonstrating the protective effect of 5-alpha-reductase inhibitors (5ARi) for men with COVID-19.¹⁷ In a study of 77 men hospitalized with COVID-19 we found among men taking 5ARis, 8% were admitted to the ICU compared to 58% of men not taking 5ARis ($P = 0.0015$). In the cohort, 5ARis were associated with reduced risk for ICU admissions RR 0.14 (95% CI: 0.02–0.94).¹⁷ Similarly, we have demonstrated that the frequency of COVID-19 symptoms was drastically reduced for men using 5ARis in an outpatient setting. A statistically significant ($p < 0.05$) reduction in the frequency of 20 of the 29 clinical symptoms was observed in AGA men using 5ARis compared to AGA men not using 5ARis. For example, 38% and 2% of men presented with low-grade fever, 60% and 6% with dry cough, and 88% and 15% reported anosmia in the non-5ARi and 5ARi groups, respectively.¹⁸

One limitation of 5ARis is the time course required to achieve systemic DHT reductions. As such, we explored the use of a novel second generation androgen receptor antagonist Proxalutamide as a means for rapid reduction in AR activity. Proxalutamide (GT0918) demonstrates a dual mechanism of action. It is highly effective in inhibiting AR as well as exhibiting pharmacological effects of inducing the down-regulation of AR expression; the

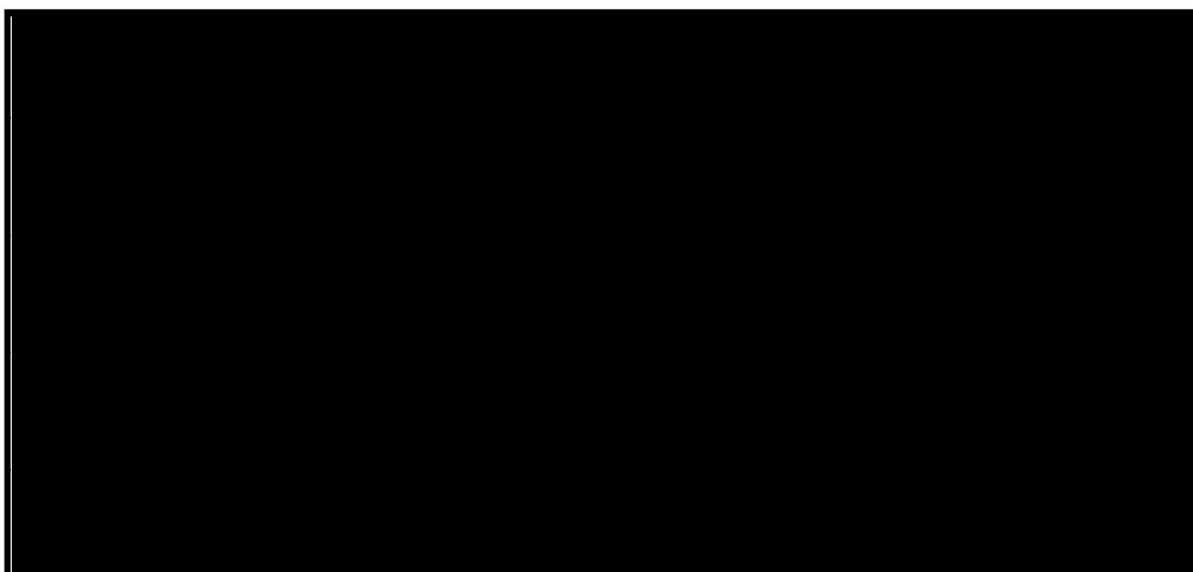
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mechanism that is not present in bicalutamide and enzalutamide. Because of the dual mechanism of action, it is expected to be a more effective and less toxic second-generation anti-androgen drug therapy. Clinical evidence has demonstrated that Proxalutamide lowers AR expression and activity. Additionally, it has been reported that Proxalutamide lowers the expression of ACE2. Both would be beneficial for preventing SARS-CoV-2 entry into lung cells.

1.1. Investigational Drug

Proxalutamide (200 mg) q.d.



Proxalutamide (GT0918) demonstrates a dual mechanism of action. It is highly effective in inhibiting AR as well as exhibiting pharmacological effects of inducing the down-regulation of AR expression; the mechanism that is not present in bicalutamide and enzalutamide. Because of the dual mechanism of action, it is expected to be a more effective and less toxic second-generation anti-androgen drug therapy. Clinical evidence has demonstrated that Proxalutamide lowers AR expression and activity. Additionally, it has been reported that Proxalutamide lowers the expression of ACE2. Both would be beneficial for preventing SARS-CoV-2 entry into lung cells.

The Proxalutamide tablets (100mg per tablet) will be manufactured by:



1.1. Pre-Clinical and Prior Clinical Data

1.1.1. Prior Pre-Clinical and Clinical Safety Data

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No prior pre-clinical safety data exists as to the use of Proxalutamide for the treatment of COVID-19; however, pre-clinical studies have been conducted in support of the US FDA IND approval of Phase-1 human trials of Proxalutamide in castration resistant prostate cancer. Selected pre-clinical animal studies conducted with Proxalutamide are provided below.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

1.1.2 Prior Clinical Safety Data

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

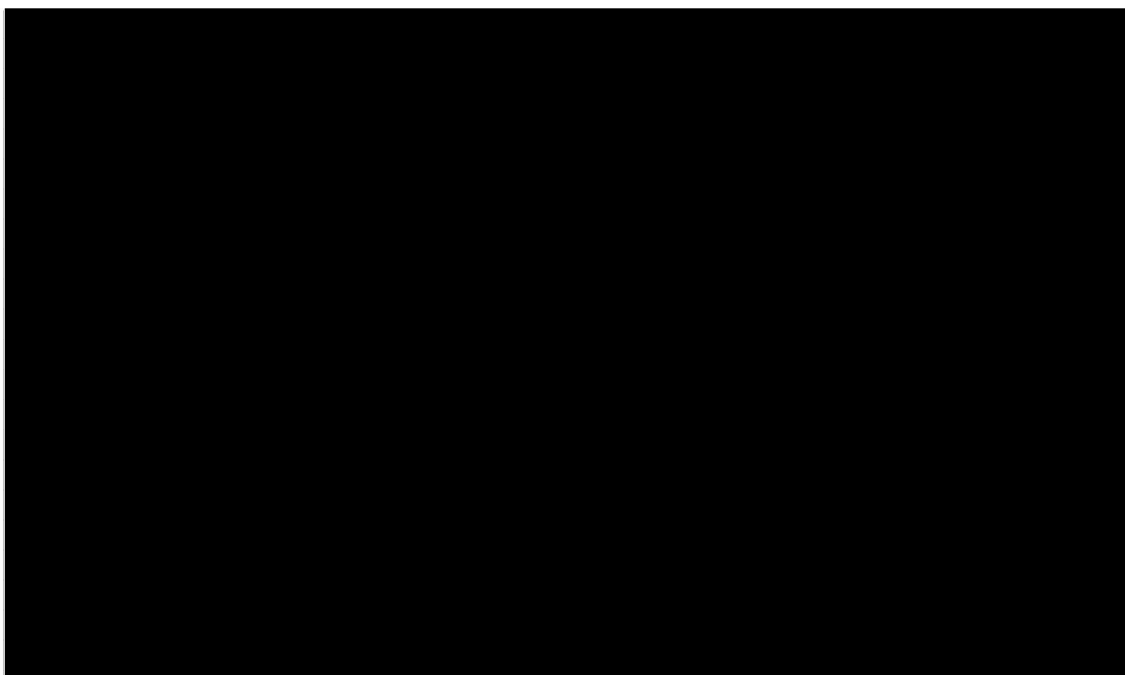
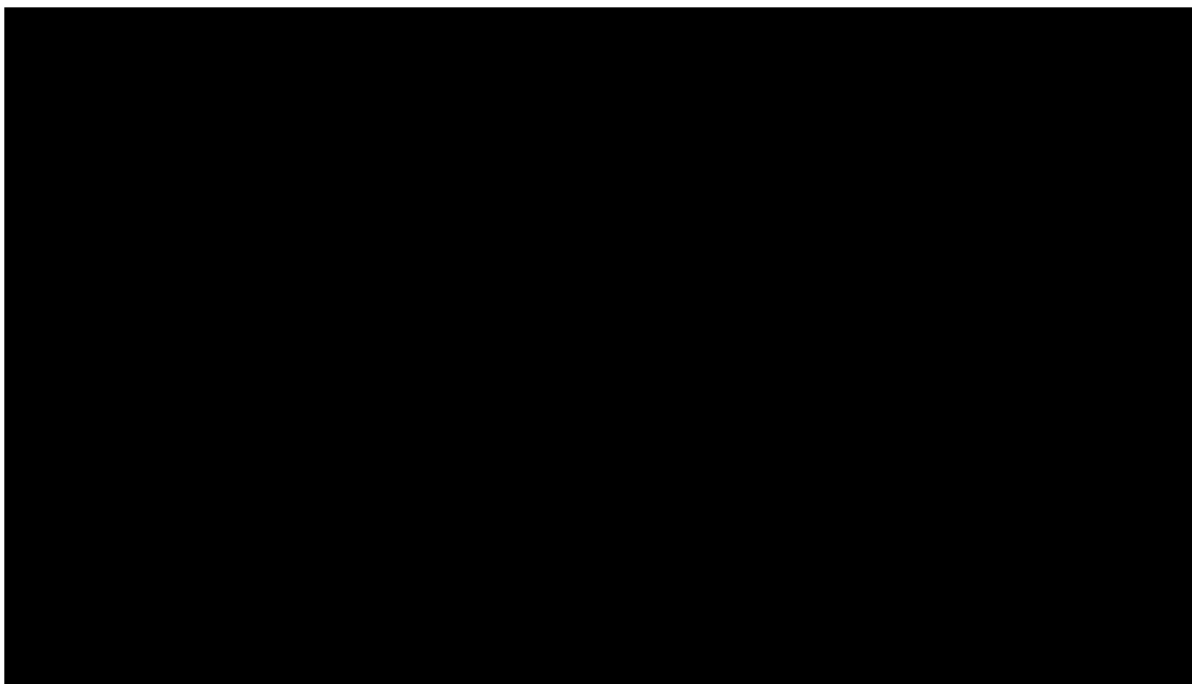
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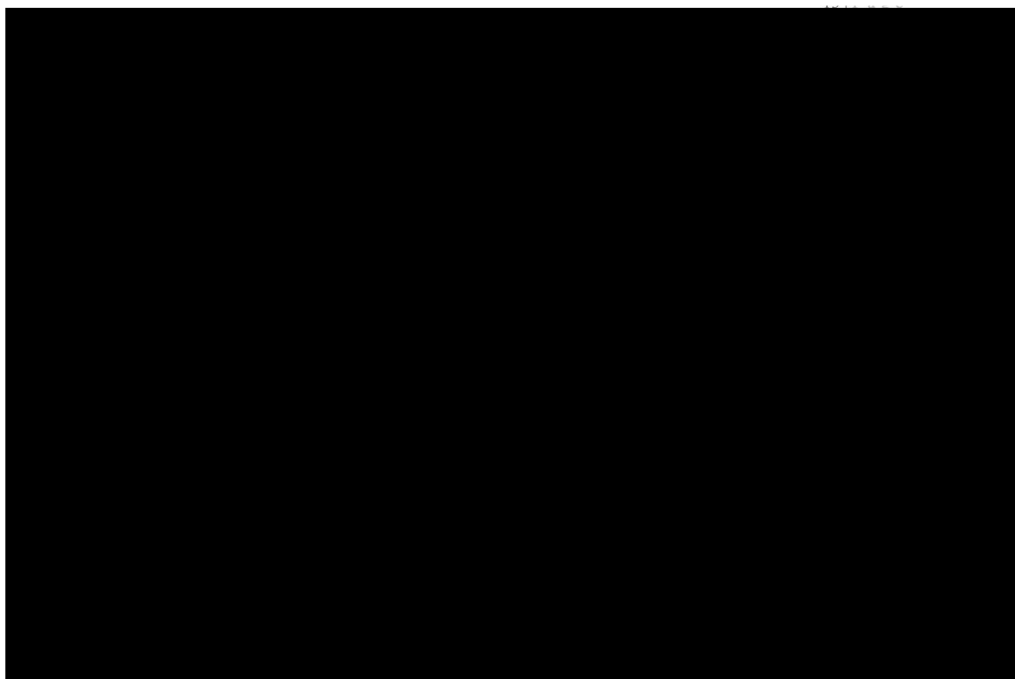
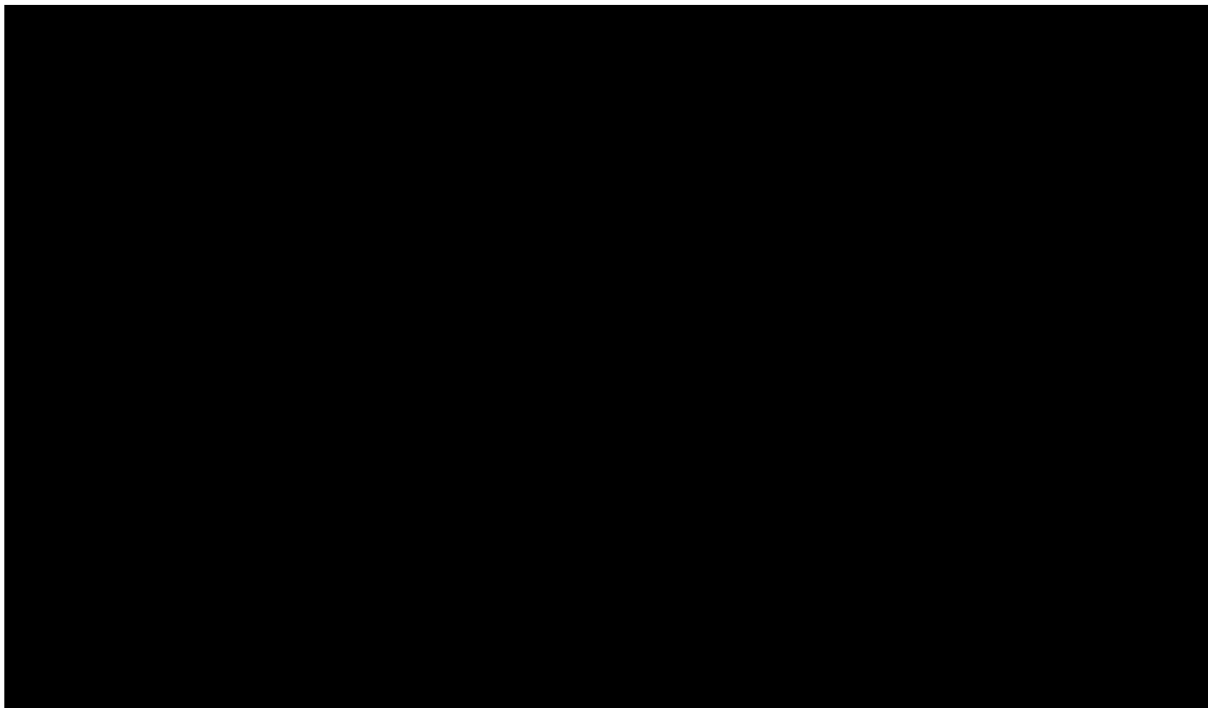
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[REDACTED]

[REDACTED]

The results indicate that there is an inhibitory effect of Proxalutamide on CYP3A4 in vitro and the corresponding in vivo drug interaction potential needs to be further investigated.

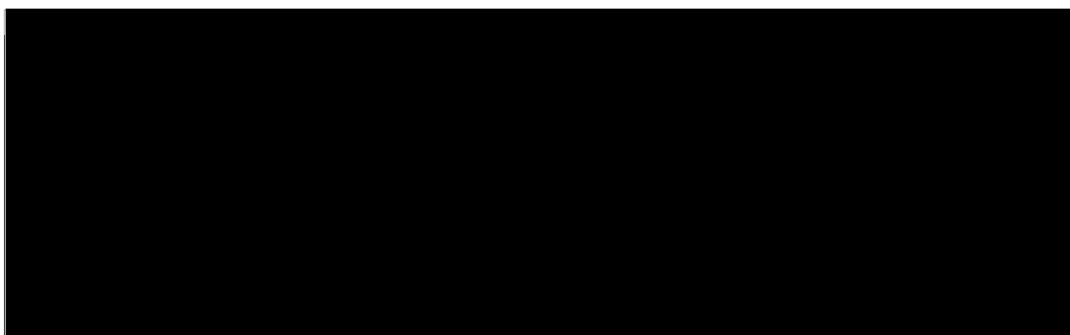
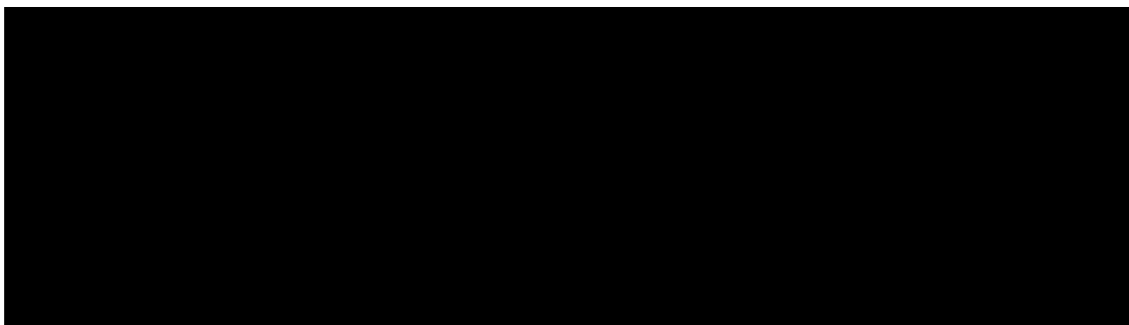
*No interaction has been reported between Proxalutamide, nitazoxanide, and azithromycin.

[REDACTED]

Proxalutamide was evaluated for induction of drug metabolizing enzymes in primary human hepatocytes. No inductive effects on CYP1A2 and CYP3A4 were observed in the level of enzymatic activity.

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Specific Populations

Pediatric

Proxalutamide pharmacokinetics have not been investigated in subjects younger than 18 years.

Geriatric

No dose adjustment is necessary in the elderly. The pharmacokinetics and pharmacodynamics of Proxalutamide were evaluated in 40 patients with an average age of 70.1 (Study 2, Section 1.1.2.4.).

Gender



Race

The effect of race on Proxalutamide pharmacokinetics has not been studied.

Renal Impairment

The effect of renal impairment on Proxalutamide pharmacokinetics has not been studied.

Hepatic Impairment

The effect of hepatic impairment on Proxalutamide pharmacokinetics has not been studied.

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1.1.3 Prior Pre-clinical Efficacy Data

No prior pre-clinical data exists as to the use of Proxalutamide as a treatment for COVID-19.; however, two studies highlight the possible benefit of the dual anti-androgen activity of Proxalutamide .

Proxalutamide inhibition of androgen binding to AR and AR protein expression

A study by Zhou et al¹⁹ reported that: “GT0918 inhibited the binding of androgen to AR in a dose-dependent manner, and the K_i value of GT0918 (1.4×10^{-8} M) in binding to AR was 3.4-fold lower than that of MDV3100 (4.8×10^{-8} M) (Fig. 1A). It indicated that GT0918 was more potent than MDV3100 in inhibiting the binding of androgen to AR.” Additionally, in cultures of C4-2B cells, “the protein expression of AR was significantly reduced by GT0918”. Data depicting the inhibition androgen binding to AR and the reduced AR protein expression in C4-2B cells is shown below:

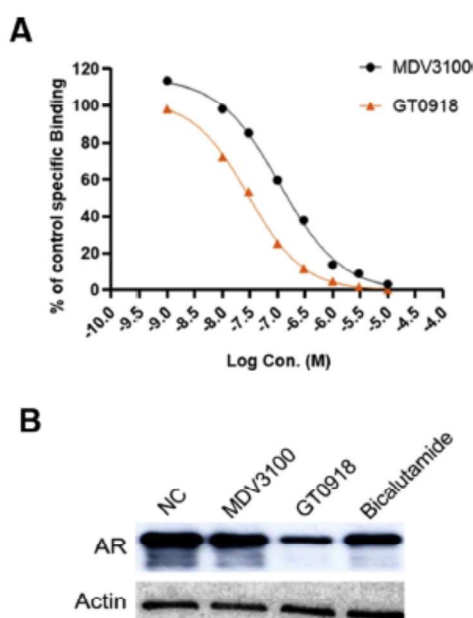


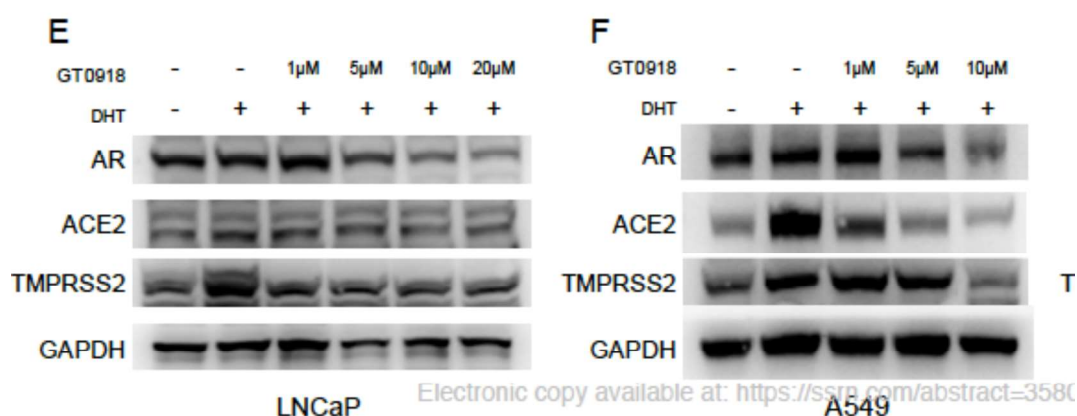
Fig. 1. GT0918 effectively decreases androgen binding to AR. (A) IC_{50} values for GT0918 and MDV3100 in inhibiting androgen from binding to AR. (B) GT0918 reduces the protein expression of AR in C4-2B cells.

Proxalutamide suppression ACE2 and TMPRSS2 in A549 lung cells

A study by Wu et al²⁰ reported that “In LNCaP and A549 cells, we showed that androgen induced the ACE2 and TMPRSS2 expression, and GT0918 could suppress the ACE2 and TMPRSS2 expression”. The data from the study is depicted in the figure below.

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1.1.4 Justification for Dosage

[REDACTED]

[REDACTED]

1.1.5 Other Data

The PI has not identified any additional data related to the safety or efficacy of this study.

1.2. Risks/Benefits

This study is designed as a prospective, interventional, placebo controlled, double-blinded, randomized parallel assignment study to assess the efficacy of Proxalutamide as a treatment for COVID-19; therefore, we assess below the risks/benefits for the proposed study.

Benefit(s) of the Proposed Clinical Study

The study is intended to explore the theory that COVID-19 infection and disease severity is driven by androgens. As such, anti-androgen therapy is hypothesized to provide protection against COVID-19 disease progression. Provided anti-androgen therapy is effective, subjects enrolled in this study will possibly experience mild COVID-19 related symptoms.

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Risk(s) of the Proposed Clinical Study

Treatment with any drug carries risk. Treatment with Proxalutamide carries the risk of the adverse events reported in Phase I clinical trials with Proxalutamide; however, due to the short treatment duration of 15 days, we believe the risk of serious adverse events is lower than described in Phase I studies.

1.3. Trial Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (Ethics Committee), and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB (EC) except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB (EC) as soon as possible.

1.4. Population

This is a multi-center study to be conducted at outpatient clinics. This exact protocol will be followed at each site. There will be one PI. The study will be approved by the national Ethics Committee.

The population for this study will be non-hospitalized SARS-CoV-2 confirmed subjects previously presented to an outpatient hospital and/or clinic participating in the local health care electronic record exchange (SUS). Approximately, 260 male subjects who meet all the eligibility criteria will be enrolled. The estimated time from screening to end of the study for each subject is approximately 30 days.

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2. Trial Objectives

The primary purpose of this study is to evaluate the efficacy of Proxalutamide as a treatment for COVID-19.

3. Trial Design

3.1 Primary Study Endpoints/Secondary Endpoints

Primary Outcome Measures:

1. COVID-19 hospitalization [Time Frame: 30 days]
Percentage of subjects hospitalized due to COVID-19

Secondary Outcome Measures:

1. COVID-19 Ordinal Outcomes Scale on Day 15, 30 [Time Frame: assessed on study day 15, 30]

We will determine the COVID Ordinal Scale for all patients on study day 15, 30

COVID Ordinal Scale defined as:

8. Death;
7. Hospitalized, on invasive mechanical ventilation or ECMO;
6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
5. Hospitalized, requiring supplemental oxygen;
4. Hospitalized, not requiring supplemental oxygen- requiring ongoing medical care (COVID-19 related or otherwise);
3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
2. Not hospitalized, limitation on activities;
1. Not hospitalized, no limitations on activities

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3.2 Study Design/Type

This study is designed as a prospective, interventional, placebo controlled, double-blinded, randomized parallel assignment study. The study will have 2 arms:

For the first 15 days:

Arm 1: Subjects administered Proxalutamide 200mg q.d for 15 days (or until remission) + standard of care as determined by the PI at the site

Arm 2: Subjects administered Proxalutamide placebo q.d for 15 days (or until remission) + standard of care as determined by the PI at the site

Starting at day 15 +/- 3 (if patients have not experienced full remission)

Arm 1: Subjects administered Proxalutamide placebo 200mg q.d for 15 days (or until remission) + standard of care as determined by the PI at the site

Arm 2: Subjects administered Proxalutamide placebo 200mg q.d for 15 days (or until remission) + standard of care as determined by the PI at the site

Study Environment:

This is a multi-center study to be conducted at multiple outpatient clinics (the sites). This exact protocol will be followed during the study. There will be one or more PIs. The study will be approved by the appropriate Ethics Committees (IRBs). Data collection will be performed at each site by study personnel under the supervision of the PI.

Study Design:

Phase I: Enrollment (first site visit or consultation by phone):

1. Each subject will be evaluated for the inclusion and exclusion criteria
2. Each subject will undergo a physical examination
3. Each subject (or legally authorized representative) will complete and sign the Informed Consent Form
4. Each subject will be assigned a subject study number
5. Each subject will be randomly assigned to an Arm (Section 3.3)
6. Based on the Arm assignment, each subject will be given a 15 days supply of the intervention

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7. All information will be recorded in the appropriate CRFs

Phase II: Treatment Administration at Home (day 0-15)

1. Each subject will self-administer the assigned treatment orally once per day

Phase III: Outcome Assessment at Site (day 15+/-3):

1. Each subject will be evaluated by the PI for the primary and secondary outcomes

2. The PI will assess each subject for any treatment related adverse events

3. All information will be recorded in the appropriate CRFs

Phase IV: Treatment Administration at Home (day 16-30)

1. Each subject will self-administer the assigned treatment orally once per day

Phase V: Outcome Assessment at Site (day 30+/-3):

1. Each subject will be evaluated by the PI for the primary and secondary outcomes

2. The PI will assess each subject for any treatment related adverse events

3. All information will be recorded in the appropriate CRFs

3.3 Randomization

Subjects will be randomized into 1 of 2 arms each will receive an interventional treatment.

For the first 15 days:

Arm 1: Subjects administered Proxalutamide 200mg q.d for 15 days (or until remission) + standard of care as determined by the PI at the site

Arm 2: Subjects administered Proxalutamide placebo q.d for 15 days (or until remission) + standard of care as determined by the PI at the site

Starting at day 15 +/- 3 (if patients have not experienced full remission)

Arm 1: Subjects administered Proxalutamide placebo 200mg q.d for 15 days (or until remission) + standard of care as determined by the PI at the site

Arm 2: Subjects administered Proxalutamide placebo 200mg q.d for 15 days (or until remission) + standard of care as determined by the PI at the site

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During the enrollment phase (admission to hospital), each subject will be assigned a subject study number. The first subject will be assigned the number 001 and each subject thereafter will be assigned a consecutive number i.e., 002, 003, etc. The randomization plan is based on a 1:1 ratio for each arm. Since the study is double-blinded, the following randomization schedule will be used but the identification of the Arm assignment will be known only to the sponsor:

Subjects 001-020 will be assigned to Arm 1
 Subjects 021-040 will be assigned to Arm 2
 Subjects 041-060 will be assigned to Arm 1
 Subjects 061-080 will be assigned to Arm 2
 Subjects 081-100 will be assigned to Arm 1
 Subjects 101-120 will be assigned to Arm 2
 etc.....

3.4 Records

Each subject will be assigned a number. The numbers will be consecutive starting at 001.

A record will be created for each subject. Each record will contain a medical history, and the subject's efficacy parameters copied from the subject's charts and documented in the appropriate CRF.

The subjects' records will be stored and handled in the same manner as the PI's other clinical study patients' records are stored i.e., in a locked research storage area.

No other data will be recorded. No personal information will be kept outside the study site.

Data compiled at the end of the study will not include any information that can be used to identify individuals.

3.5 Duration

The duration of the study is 30 days. There will be no study related follow-up treatment.

3.6 Discontinuation

In the event that a subject experiences a SAE or an AE grade 3 or 4 (defined in Section 6) we will discontinue the study for that particular subject.

In the event a subject in any arm experiences a SAE defined as death not due to respiratory failure (presents with clear lung CT and no ARDS symptoms) the study will be discontinued. The remainder of the study shall continue.

3.7 Product Accountability

All interventional treatments for this study will be stored and monitored according to each hospital standard protocol.

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3.8 Data Identification

The subject records kept by the PI will be stored and handled in the same manner as the PI's other clinical research subject records. Only authorized personnel named in this study, or medical professional retained by the PI in case of an adverse event, will have access to the subject records.

No other data will be recorded. No personal information will be kept outside the study site.

Data compiled at the end of the study will not include any information that can be used to identify individuals.

4. Selection and Withdrawal of Subjects

4.1 Inclusion Criteria

1. Male age ≥ 18 years old
2. Laboratory confirmed positive SARS-CoV-2 rtPCR test within 7 days prior to randomization
3. Clinical status on the COVID-19 Ordinal Scale (defined in Section 5.1) of 1 or 2
4. Coagulation: $\text{INR} \leq 1.5 \times \text{ULN}$, and $\text{APTT} \leq 1.5 \times \text{ULN}$
5. Subject (or legally authorized representative) gives written informed consent prior to any study screening procedures
6. Subject (or legally authorized representative) agree that subject will not participate in another COVID-19 trial while participating in this study

4.2 Exclusion Criteria

1. Subject enrolled in a study to investigate a treatment for COVID-19
2. Subject taking an anti-androgen of any type including: androgen deprivation therapy, 5-alpha reductase inhibitors, etc...
3. Patients who are allergic to the investigational product or similar drugs (or any excipients);
4. Subjects who have malignant tumors in the past 5 years, with the exception of completed resected basal cell and squamous cell skin cancer and completely resected carcinoma in situ of any type
5. Subjects with known serious cardiovascular diseases, congenital long QT syndrome, torsade de pointes, myocardial infarction in the past 6 months, or arterial thrombosis, or unstable angina pectoris, or congestive heart failure which is classified as New York Heart Association (NYHA) class 3 or higher, or left ventricular ejection fraction (LVEF) $< 50\%$, QTcF > 450 ms
6. Subjects with uncontrolled medical conditions that could compromise participation in the study (e.g. uncontrolled hypertension, hypothyroidism, diabetes mellitus)
7. Known diagnosis of human immunodeficiency virus (HIV), hepatitis C, active hepatitis B, treponema pallidum (testing is not mandatory)
8. Alanine Transaminase (ALT) or Aspartate Transaminase (AST) > 5 times the upper limit of normal.
9. Estimated glomerular filtration rate (eGFR) < 30 ml/min
10. Severe kidney disease requiring dialysis

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11. Subject unlikely to return for day 15 site visit for reasons other than remission
12. Subject (or legally authorized representative) not willing or unable to provide informed consent

4.3 Subject Withdrawal

Subjects may withdraw at any time for any reason. In the event the principal investigator or the site monitor believes a subject is at risk of injury the subject will be withdrawn from the study and:

- (a) If the subject has not completed the study
- (b) The subject will be replaced with another subject
- (c) The PI will follow-up with the subject every day for 14 days
- (d) The information will be reported in the appropriate CRF

4.4 Treatment of Subjects

Once enrolled in the study, each subject will self-administer the assigned treatment at home in the form of a daily oral tablet.

4.5 Medication

Proxalutamide showed no significant inhibition on CYP1A2 and CYP2E1, weak inhibition on CYP2D6, CYP2C9, CYP2C19 and CYP3A (midazolam), but obvious inhibition on CYP3A4 (testosterone). Potential inducer on CYP3A4 at a concentration of 10µM. No inductive effects on CYP1A2 and CYP2B6 were observed in the level of enzymatic activity. Co-administration of strong/moderate CYP3A4 inducer, strong/moderate CYP3A4 inhibitor, sensitive CYP3A4/ CYP2D6 substrates and narrow therapeutic index with Proxalutamide should be used cautiously (See Appendix 1).

Note: No interaction has been reported between Proxalutamide, Nitazoxanide, and azithromycin.

4.6 Monitoring for subject compliance

During each site visit, the PI will ask each subject to confirm if he adhered to the daily administration of the treatment.

5 Assessment of Efficacy

5.1 Efficacy Parameters

The following efficacy parameters will be assessed and recorded in the CRF.

I. COVID-19 Hospitalization:

1. COVID-19 hospitalization [Time Frame: 30 days]
Percentage of subjects hospitalized due to COVID-19

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II. COVID-19 Ordinal Outcome Scale:

1. COVID-19 Ordinal Outcomes Scale on Day 15, 30 [Time Frame: assessed on study day 15, 30]

We will determine the COVID Ordinal Scale for all patients on study day 15, 30

COVID Ordinal Scale defined as:

8. Death;
7. Hospitalized, on invasive mechanical ventilation or ECMO;
6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
5. Hospitalized, requiring supplemental oxygen;
4. Hospitalized, not requiring supplemental oxygen- requiring ongoing medical care (COVID-19 related or otherwise);
3. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
2. Not hospitalized, limitation on activities;
1. Not hospitalized, no limitations on activities

5.2 Method and Timing

The assessments, as described in section 5.1, will occur as follows:

The PI will assesses each subject and record the efficacy parameters at baseline, days 15 and 30 following enrollment (+/-3 days).

6 Assessment of Safety

6.1 Safety Parameters

Safety parameters will be assessed as follows:

I. Physical Examination:

The PI will conduct a thorough physical examination during screening. The assessment will be recorded in the appropriate CRF.

II. Adverse Events:

Safety will be assessed by summarizing the incidence and type of Adverse Events in a CRF form.

6.2 Method and Timing

The assessments, as described in section 6.1, will occur as follows:

I. Physical Examination

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The assessment will occur at screening. The information will be recorded in the appropriate CRF.

II. Adverse Events:

Adverse events will be assessed by the PI at baseline and during the site visits on days 15 and 30 following enrollment (+/-3 days).

The methods employed for completing assessments are described in section 6.1

6.3 Adverse Events

6.3.1 Definition of Adverse Event (AE)

AE means any medical event associated with the use of an intervention, whether or not considered intervention-related. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

Given the nature of severity of the underlying illness, subjects will have many symptoms and abnormalities in vitals and laboratory. All Grade 3 and 4 AEs will be captured as AEs in this trial.

6.3.2 Definition of Serious Adverse Event (SAE)

An SAE is defined as “An AE or suspected adverse reaction is considered serious if, in the view of either the investigator or the sponsor, it results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.” “Life-threatening” refers to an AE that at occurrence represents an immediate risk of death to a subject. An event that may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered a SAE. All SAEs, as with any AE, will be assessed for severity and relationship to study intervention. All SAEs will be recorded on the appropriate SAE

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CRF. All SAEs will be followed through resolution or stabilization by a licensed study physician (for IND studies, a physician listed on the Form FDA 1572 as the site PI or Sub-Investigator). All SAEs will be reviewed and evaluated by DMID and will be sent to the SMC (for periodic review), and the IRB/IEC.

6.3.3 Suspected Unexpected Serious Adverse Reactions (SUSAR)

A SUSAR is any SAE where a causal relationship with the study product is at least reasonably possible but is not listed in the Investigator Brochure (IB), Package Insert, and/or Summary of Product Characteristics.

6.3.4 Classification of an Adverse Event

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This includes but is not limited to physicians, physician assistants, and nurse practitioners.

6.3.5 Severity of Adverse Events

All AEs and SAEs will be assessed for severity, according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017). For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.

Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

Severe (Grade 4): Events that are potentially life threatening.

AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop Duration of each reported AE will be recorded on the appropriate CRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

6.3.6 Relationship to Study Intervention

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For each reported adverse reaction, the PI or designee must assess the relationship of the event to the study product using the following guideline:

Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

6.3.7 Time Period and Frequency for Event Assessment and Follow-Up

For this study, all Grade 3 and 4 AEs and all SAEs occurring from the time the informed consent is signed through the Day 30 (end of study) visit will be documented, recorded, and reported.

6.3.8 Investigators Reporting of AEs

Information on all AEs should be recorded on the appropriate CRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

6.3.9 Serious Adverse Event Reporting

6.3.9.1 Investigators Reporting of SAEs

Any AE that meets a protocol-defined criterion as a SAE must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group, at the following address:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20817, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US) SAE FAX
Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US) SAE Email Address:
PVG@dmidcroms.com

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible. The DMID

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Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct. At any time after completion of the study, if the site PI or appropriate sub-investigator becomes aware of an SAE, the site PI or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

6.3.9.2 Regulatory Reporting of SAEs

Following notification from the site PI or appropriate sub-investigator, DMID, as the IND sponsor, will report any SUSAR in an IND safety report to the FDA and will notify all participating site PIs as soon as possible. DMID will report to the FDA any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. If the event is not fatal or life-threatening, the IND safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request. SAEs that are not SUSARs will be reported to the FDA at least annually in a summary format which includes all SAEs. Sites may have additional local reporting requirements (to the IRB and/or national regulatory authority).

6.3.10 Reporting Events to Subjects

Subjects will be informed of any severe AEs or SAEs that occur as part of their participation in this trial.

6.3.11 Reporting of Pregnancy

Pregnancy is not defined as an AE. However, any pregnancy that occurs during study participation should be reported to the sponsor on the appropriate CRF. Pregnancy should be followed to outcome.

6.4 *Unanticipated Problems*

6.4.1 Definition of Unanticipated Problems (UP)

An Unanticipated Problem is any event, incident, experience, or outcome that meets the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

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- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.4.2 Unanticipated Problem Reporting

To satisfy the requirement for prompt reporting, unanticipated problems (UP) will be reported using the following timeline: UPs that are SAEs will be reported to the IRB and to the Statistical and Data Coordinating Center (SDCC)/study sponsor within 24 hours of the investigator becoming aware of the event per the above describe SAE reporting process. Any other UP will be reported to the IRB and to the SDCC/study sponsor within 3 days of the investigator becoming aware of the problem.

6.4.3 Reporting Unanticipated Problems to Subjects

Subjects will be informed of any UPs that occur as part of their participation in this trial.

7 Statistical Plan

7.1 Statistical Methods

I. General Principles:

- Double-blinded, placebo controlled randomized interventional study with a two-sided type I error rate of 0.05.
- Continuous variables will be expressed as median (interquartile range [IQR]) and categorical variables will be expressed as a number
- 95% confidence intervals will be calculated for the primary outcome
- Group comparisons will be analyzed by the Wilcoxon rank sum test or χ^2 test for independent proportions
- The placebo arm will be used as a reference group when calculating treatment effects
- Differences between rates of clinical improvement will be calculated using unadjusted ordinal logistic regression or Cox proportional hazard models
- Statistical analyses will be conducted using XLSTAT version 2020.5.1 (Addinsoft, Inc.)

II. Statistical Hypotheses:

The primary endpoint is the proportion of subjects hospitalized through day 30. The primary outcome will be analyzed using the χ^2 test for independent proportions.

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The Null Hypothesis (H_0) is that the proportion of subjects hospitalized due to COVID-19 in Arm 1 (Proxalutamide) is equal to the proportion of subjects hospitalized due to COVID-19 in Arm 2 (standard of care)

The Alternative Hypothesis (H_A) is that the proportion of subjects hospitalized due to COVID-19 in Arm 1 (Proxalutamide) is less than the proportion of subjects hospitalized due to COVID-19 in Arm 2 (standard of care)

Mathematically written as:

$$H_0: p_1 - p_2 = 0$$

$$H_A: p_1 - p_2 < 0$$

Where p_1 and p_2 are the proportion of subjects hospitalized from arm 1 and arm 2 respectively.

III. Primary Efficacy Analysis:

- The χ^2 test for independent proportions will be used to assess the primary end point.
- P-values < 0.05 will be considered significant. All statistical analysis will be based on the intent-to-treat (ITT) population. All missing data will be described.

7.1 Sample Size Estimates

Assumptions:

- Riccardo et al (2020)¹ reported that in Italy the hospitalization rate was as high as 20% among adults above the age of 65 tested positive for SARS-CoV-2. Further, Montopoli et al (2020)² reported that males represent 60% of hospitalized patients; therefore, we can estimate that the rate of hospitalization of males over the age of 65 tested positive for SARS-CoV-2 is approximately 30%.
- To estimate the efficacy of Proxalutamide as a treatment for COVID-19, we use the results reported by Montopoli et al (2020)². According to Montopoli et al: “Comparing the total number of SARS-CoV-2 positive cases, patients with prostate cancer receiving ADT had a significantly lower risk of SARS-CoV-2 infections compared to patients who did not receive ADT (OR 4.05; 95% CI 1.55-10.59). Applying the 20% hospitalization rate, we derive a probability of treatment efficacy of 50%”

$$p_{\text{treatment}} = \frac{OR \times p_{\text{control}}}{1 + OR \times p_{\text{control}} - p_{\text{control}}} :$$

- The study has two arms with randomization at 1:1 ratio
- 80% power to detect the difference in proportions using a two-tailed test with a type I error rate of 5%

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- 5% of the subjects will not complete the study.

Sample Size Estimate:

Based on the assumptions above, we calculated³ that at a minimum we would need to recruit 254 subjects i.e., 127 subjects in each arm

References:

1. <https://doi.org/10.1101/2020.04.08.20056861>
2. Montopoli M, Zumerle S, Vettor R, Rugge M, Zorzi M, Catapano CV, Carbone GM, Cavalli A, Pagano F, Ragazzi E, Prayer-Galetti T, Alimonti A, Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (n=4532), *Annals of Oncology* (2020), doi: <https://doi.org/10.1016/j.annonc.2020.04.479>.
3. <https://jamanetwork.com/journals/jama/fullarticle/2765184>
4. Machin D, Campbell MJ, Tan SB, Tan SH (2009) *Sample size tables for clinical studies*. 3rd ed. Chichester: Wiley-Blackwell.

7.2 Subject Population(s) for Analysis

- The primary analysis will be based on the intent-to-treat (ITT) population. The data from all subjects enrolled in the study will be analyzed.
- The safety analysis will be based on a modified intent-to-treat (MITT) population i.e., subjects who received at least one dosage of the interventional treatment.
- Subgroup analysis based on: 1) age stratification; and 2) androgen status as defined by the “Gabrin sign” will be conducted for the primary and secondary outcomes.

7.4 Interim Analysis

Interim efficacy and safety data will be made upon recruitment of 50% of the subjects.

7.5 Termination Criteria

Upon occurrence of any one of the events listed below, the study will terminate or be modified accordingly:

- Completion of the study by a sufficient number of subjects (254 subjects) to reach our confidence level
- Termination of Arm 1: Serious adverse event due to treatment with Proxalutamide

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- Substantial evidence of treatment difference between the arms. The study design will be modified to an open-label study.

7.6 Accountability Procedure

The data will be analyzed by a bio-statistics expert. The data will also be independently verified by an outside expert consultant.

7.7 Deviation Reporting

No deviation from the plan will be implemented without the prior review and approval of the EC/IRB.

8 Direct Access to Source Data/Documentation

The PI and hospital will permit trial-related monitoring, audits, IRB/IEC(s) review and regulatory inspection(s) by providing direct access to source data/documentation.

9 Quality Control and Quality Assurance

Every effort will be made to keep staff assignments consistent throughout the entire study. The PI who assesses the subject at baseline should follow the subject throughout the completion of the study. This will ensure that this study is conducted – and that data is generated, documented (recorded), and reported - in compliance with this protocol, with GCP, and any other applicable regulatory requirements. The study monitor will audit the study procedures and CRFs throughout the study.

10 Ethical Considerations

This study will be conducted according to US and international standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and FDA guidance E6) for all studies. Applicable government regulations and hospital research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the Institutional Review Board (IRB) for formal approval to conduct the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11 Data Handling and Record Keeping

During enrollment, each subject will be assigned a number. The numbers will be consecutive starting at 001.

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During enrollment a record will be created for each subject. Each record will contain the subject's demographics, subject's efficacy parameters and any adverse events or study related information.

The subjects' records will be stored and handled in the same manner as the PI's patients' records.

The study monitor will keep a separate record at the monitor's office of each subject's identification number, the treatment administered to the subject (arm assignment), outcomes and any laboratory results.

No other data will be recorded. No personal information will be kept outside the study site.

Data compiled at the end of the study will not include any information that can be used to identify individuals.

The site will keep all subject records for a minimum of 3 years after the completion of the study.

12 Finance and Insurance

The Principal Investigator will be responsible for the cost of study. The site carries insurance for accidental injury. There is no other insurance.

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APPENDIX 1

Strong CYP3A4 inducer
Avamibe, Carbamazepine, Phenytoin, Rifampicin, Mitotan, Nevirapine, Phenobarbital, Rifabutin, Rifapentine, St. John's wort, Alfentanil, Ryclosporin, Dihydroergotamine / Ergotamine, Fentanyl, Irinotecan, Pimozit, Quinidine, Sirolimus, Tacrolimus
Moderate CYP3A4 inducer
Smacet, Tavern, Bosentan, Efaviron, Etruverin, Lopinavir, Modafinil, Nafcillin, Thalidazine, Tiranavir, Ritonavir
Strong CYP3A4 inhibitor
Posidovir, Clarithromycin, Conivatan, Indinavir, Itraconazole, Ketoconazole, lopinavir / Ritonavir, Mibedil, Nefazodone, Nefenavir, Posaconazole, Ritonavir, Saquinavir, Trapivir, Taliomycin, Voriconazole, Etigavir / Ritonavir, Fluconazole, Tiranavir / Ritonavir, Acetamycin
Moderate CYP3A4 inhibitors
Apronavir, Aripitan, Azanavir, Casopitam, Cimetidine, Ciprofloxacin, Clazotinib, Cyclosporin, Dalunavir, Diltiazem, Dronedarone, Erythromycin, Imatinib, Tofesoyang, Verapamil
Sensitive CYP3A4 substrates
Remifentanil, Aripiptam, Budesonide, Buspirone, Conivatan, Daphnesin, Darunavir, Dasatinib, Dronedarone, Eletroptan, Eplerenone, Everolimus, Felodipine, Indinavir, Fluticasone, Lopinavir, Lovastatin, Lulasidone, Maravelo, Midazolam, Nisoldipine, Quetiapine, Saquinavir, Sildenafil, Simvastatin, Sirolimus, Tolvaptan, Tiranavir, Triazolam, Vardenafil
Narrow therapeutic index CYP3A4 Substrate
Astemizole, Cisapride, Cyclosporine, Dihydroergotamine, Fentanyl, Pethidine, Quinidine, Tacrolimus, Terfenadine
Sensitive CYP2D6 substrates

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Tomoxetine, Decipamine, Dextromethorphan, Metoprolol, Nebeprolol,	Perphenazine,
Tolterodine, Venlafaxine, Avamibe, Carbamazepine,	Phenytoin sodium, Rifampicin

Narrow therapeutic index CYP2D6 Substrate

Thioridazine

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